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Antibodies to deamidated gliadin predict celiac disease in an infant with intestinal intussusception: A case report

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Abstract

The diagnosis of Celiac Disease (CD) in the first year of life can be challenging because of the clinical presentation, the other possible causes of malabsorption in infants and the suboptimal sensitivity of anti-tissue transglutaminase antibodies (tTG) at this age. We report a female 14-month-old child who was evaluated for failure to thrive (<3rd percentil) and occasional abdominal pain. Screening for CD revealed negative IgA anti-tTG and IgA anti-endomysial (EMA) in presence of normal serum IgA levels, but positive IgG anti-gliadin deamidated antibodies (DGP). After 2 months, the child was hospitalised for intermittent vomiting, diarrhea and abdominal pain: an intestinal intussusception was diagnosed at abdominal ultrasound. During the stay, second serum investigation for CD revealed a high positivity for IgA anti-tTg and EMA with persistent IgG anti-DPG. Genetic test showed positivity for HLA DQ2. Introducing gluten-free diet, symptoms disappeared and the infant experienced rapid catch-up growth. This case highlights the utility of anti-DGP for early screening in infants to avoid severe complications, such as intussusception as here reported.

Keywords

Celiac disease; malabsorption; intussusception; anti-tissue transglutaminase antibodies; anti-gliadin deamidated antibodies.

Abbreviations

CD: Celiac disease; tTG: anti-tissue transglutaminase antibodies; EMA: Anti-tTG and IgA anti-endomysial; DGP: IgG anti-gliadin deamidated antibodies.

Background

Celiac disease (CD) is an autoimmune disorder triggered by gluten ingestion in genetically predisposed subjects [1] with a reported prevalence of 0.5–1% of the general population [2,3]. It is generally

accepted that adaptive immunity and imbalance between T helper 1 and 2 cell responses are key elements of the pathogenesis of this autoimmune process: CD4+ T cells recognize gliadin peptides deamidated by tissue transglutaminase in the lamina propria of the small bowel and bound to DQ2+ or DQ8+ antigen-presenting cells. The gliadine-reactive CD4+ T cells enhance an adaptive immune response that leads to intraepithelial and lamina propria infiltration of inflammatory cells, crypt hyperplasia and villous atrophy [4].

Clinically, the intestinal form of CD is more detected in the paediatric population by diarrhea, loss of appetite, abdominal distention and failure to thrive. Celiac patients could have undirected symptoms, such as anemia, irritability, lethargy, anorexia, hair loss [5]; in minor part, they can also present an asymptomatic form [6]. The association between intussusception and CD is rare. In most cases, bowel intussusception is idiopathic in children [7,8].

According to the ESPGHAN guidelines published in 2020, CD can be diagnosed without performing small-bowel biopsies in presence of normal serum of IgA, high titer (over 10 times the cut-off) of anti-tTG-IgA and detectable EMA. For the diagnostic procedure, the first step is the combination of total IgA and anti-tTg-IgA; in cases of IgA total deficit, a second investigation of IgG (DGP, EMA or TGA) [9]. Although, IgG anti-DGP may appear earlier than IgA anti-tTG in very young children with CD and IgA anti-tTG perform at a lower sensitivity and specificity in children under 18 months of age compared to older subjects, while IgG anti-DPG have the higher specificity [10].

Case Presentation

A 14-month-old female was evaluated for failure to thrive. She was delivered at 38 weeks after a normal pregnancy (birth weight 3250 gr). Familial and antenatal history was unremarkable; in particular, history of autoimmune diseases was negative. The patient had been exclusively breastfed for the first 6 months of life and then regularly weaned. Parents referred good growth and psychomotor development in the first year, but from the 12th month of age she showed weight-growth slowdown and occasional abdominal pain in absence of other gastrointestinal disorders. Routine laboratory tests revealed normal full blood count. At this time, screening for CD showed normal IgA levels, absence of IgA anti-tTG and EMA but high positivity serum anti-DGPs (IgG 292 U/mL; normal range < 10 U/ml). The child continued free diet. Other negative tests: stool culture, Clostridium Difficile testing, fecal hydrolysis for detection of no reducing carbohydrates, fecal elastase, sweat chloride test, complete metabolic panel [29]. An abdominal ultrasound showed normal images. After two months, at the age of 16 month the child was admitted to our university hospital pediatrics of Catania, Italy, for intermittent vomiting, diarrhea and abdominal distension. Her weight for-length was below the 3rd percentil. The physical examination revealed pallor, lethargy, anorexia, muscle wasting, distended but soft palpable abdomen with no abdominal pain. Laboratory tests revealed anemia (Hb: 10.8 mg/dl; normal range 12-15 mg/dl) with iron deficiency, hypoalbuminemia (3.0 g/dl; normal range 3.5-5 g/dl). Other normal laboratory tests: white cells count and platelets, glycemia, electrolytes, thyroid-stimulating hormone, creatinine kinase, aspartate transferase, alanin transferase, stool exams. Urgent abdominal ultrasound diagnosed small bowel intussusception (SBI) (Figure 1), identifing the tipical "Onionskin" image of part of the small bowel.

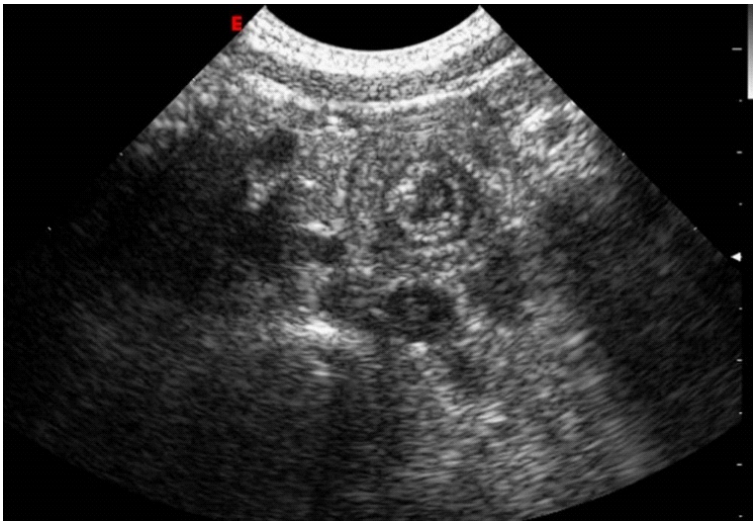

Figure 1: It is possible to observe onionskin-like imagine, suggestive of intussusception.

Thus, the child was placed in parenteral nutrition until the resolution of clinical and radiological abdomen state. During the stay, a second serum investigation for CD showed interesting results: High positivity for IgA anti-tTG (110 U/mL; normal range <10 U/ml), detectable EMA and persistent positivity for IgG anti-DPGs. Genetic analysis revealed the presence of HLA-DQ2 (DQA1*05). Final diagnosis was intestinal intussusception associated with severe presentation of CD. After 5 days of parenteral nutrition and therapeutic enema, the abdominal ultrasound showed resolution of the intussusception. She started gluten-free-diet: within 4 months, the child caught up with her original weight-for-age z-score, with complete normalization of neurological evaluation and laboratory parameters. After 6 months and for the next 2 years DGP and tTG antibodies resulted negative.

Discussion

Diagnosis of CD in children under 2 years of age is a diagnostic challenge because of the uncommon onset of symptoms shortly after weaning and the other differential diagnoses of malabsorption at this age [11]. In our case, at the beginning the young child presented occasional abdominal pain and weight-growth slowdown. Pediatric abdominal pain could be due to colic, constipation, gastroesophageal reflux, milk protein allergy, urinary tract infection [30]; although, weight-growth slowdown was initial sign of malabsorption [12]. At the first laboratory screening, only anti-DPG was detected. Similarly to our case, Lammi et al. showed that in 35 of the 48 children with CD from the Finnish DIPP study [13], serum IgG antiDGP preceded tTG positivity and appeared on average 1 year earlier [14]. This is in accordance with other evidence from literature, confirming anti-DGP as a sensitive marker in very young children [15]. In a retrospective analysis, Parizade et al recommended to follow up children with DGP-positive/tTG-negative pattern and, possibly, testing HLA, such as in our case [16].

HLADQ2/HLA-DQ8 is frequent among the general population (25–35%) and only 3% of these HLA compatible individuals could go on to develop CD [36]. Determination of HLA-DQ2/DQ8 has a limited role in the diagnosis of CD, largely related to its negative predictive value to rule out CD in patients seronegative [17]. Notably, in relation to our experience, the clinical worsening suggests to investigate the optimal timing

of DPG-positive patients follow up. Familiar anamnesis of our child was negative for autoimmune diseases. Genetic test showed susceptibility for CD, detecting HLA DQ2 in heterozygosis form. Studies show that HLA-DQ2 homozygosis confers a much higher risk (25–30%) of developing early-onset CD in infants with a first-degree family member affected by the disease.

Another important aspect of our case is the correlation between SBI and CD. SBI is a common cause of acute intestinal obstruction in the pediatric population and it is normally idiopathic. Sporadic reports have described intussusception in patients with CD [18]. The known prevalence of symptomatic SBI in children with CD is reported to be 1.2%. The pathogenesis of SBI in CD is not clear: Structural changes in epithelium, increased stiffness, diameter and altered motility in small bowel are thought to be responsible for occurrence of SBI in CD. Some studies have showed that children with SBI and CD have lower serum albumin [19] and spontaneous resolution without need of surgical intervention [20]: These findings are in accordance with our experience.

Conclusion

Our case report illustrates that anti-DPG may be the first antibody to seroconvert in very young children. So, even if the recent guidelines do not suggest performing DPG IgA or IgG as initial screening for CD, our experience underlines that they may be used for an early diagnosis in symptomatic children under 2 years of age, avoiding severe complications. In addition, SBI may reveal CD in children with failure to thrive.

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